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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/044,463	01/10/2002	Davide R. Grassetti	497872000400	9878

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Davide R Grassetti
1980 Peppermint Falls Road
Jamestown, CA 95327

EXAMINER	
MITCHELL, GREGORY W	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,463	GRASSETTI ET AL.	
	Examiner	Art Unit	
	Gregory W. Mitchell	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *3,4,7-9 and 13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,10-12 and 17-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/19/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the Election filed July 13, 2005. Claims 1-24 are pending. Claims 3-4, 7-9 and 13-16 are withdrawn from consideration. Claims 1-2, 5-6, 10-12 and 17-24 are examined herein.

Election/Restrictions

Applicant's election without traverse of the modulation of NK cells as an immune response and 6,6'-dithiodinicotinic acid as a compound in the reply filed on July 13, 2005 is acknowledged.

Claims 3-4, 7-9 and 13-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 13, 2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 5-6, 10-12 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the modulation of specific immune responses (e.g. NK killer cell activity) with specific compounds (e.g. 6,6'-dithiodinicotinic acid), does not reasonably provide enablement for the modulation of *all*

immune responses with *all* thione-forming disulfides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The recitation, "thione-forming disulfides," is seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***The Nature of the Invention***:

The rejected claim(s) is/are drawn to an invention which pertains to the modulation of *any* immune response comprising the administration of *any* thione-forming disulfide.

(2). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass the modulation of immune responses comprising the administration of *any* thione-forming disulfide. The nature of the invention is complex in that it potentially encompasses *any* disulfide and *any* immune response.

(3). ***Guidance of the Specification***:

The guidance given by the specification as to what types of thione-forming disulfides would be useful in a method of the instant invention is limited. Applicant discloses disulfides bound to heterocycles comprising nitrogens β to the disulfide as thione-forming disulfides useful in the instant invention. The specification does not teach that the scope of the invention is limited to these thione-forming disulfides, however. It is noted, for example, that claim 20 indicates that the heterocycle comprise at least one nitrogen, but the remaining claims are not limited to such a recitation. Accordingly, it is unclear whether or not a heterocycle with an oxygen or a sulfur β to the sulfide would constitute a "thione-forming disulfide". Likewise, it is unclear whether or not an alcoholic disulfide, wherein the hydroxy group is on the carbon β to the disulfide, would constitute a "thione-forming disulfide". Accordingly, the metes and bounds of the phrase "thione-forming disulfides" would not be understood by one of ordinary skill in the art.

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC,

1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate." The CAFC further clearly states "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405 (emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.. A definition by function, as we have previously indicated, does not suffice to define the genus ..." at 1406 (empahasis added).

In the instant case, "thione-forming disulfides," recited in the instant claims is purely a functional distinction. Hence, these functional recitations read on any compounds that might have recited functions. However, the specification merely provides a limited number of examples of compounds for the various kinds of functional compounds possible.

Thus, Applicant's functional language at the points of novelty fail to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicant's, neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited monopoly asserted." *General Electric Co. v. Wabash Appliance Corp.* 37 USPQ at 468 (US 1938).

(4). ***Working Examples***:

The examples show the modulation of NK cells, T cells and B cells with 6,6'-dithiodinicotinic acid.

(5). ***State of the Art***:

The state of the art with regard to the modulation of specific immune responses is developed. The state of the art with regard to the modulation of *all* immune responses is underdeveloped, however. For example, the modulation discussed in the specification is related to adaptive immunity, but does not discuss the modulation of innate immunity. There is no indication that the administration of the disulfides claimed would modulate innate immune responses.

(6). ***Predictability of the Art***:

The invention is directed to the modulation of immune responses with thione-forming disulfides in general, wherein the structure of those compounds is limited only by the function of the compounds. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully describe the genus, visualize or recognize the identity of the members of the genus, by structure, formula, or

chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members of the genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug inerteractions when and/or after adminstering to a host (e.g., a human) any compounds represented by an "thione-forming disulfides," which may encompass countless compounds. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51 in particular. *Goodman & Gilman* teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). In the instant case, in the absence of fully recognizing the identity of the member genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having the claimed functional properties in

the pharaceutical compositions herein. Furthermore, it is noted that the proposed mechanism of reaction, as set forth in the specification, is the oxidation of a thiol to a disulfide. There is no indication in the specification that such a step would be limited to those cells surfaces related to an immune response, however. Thus, it would be imperative for the skilled artisan to determine the adverse effects of unwanted disulfide formation for each of the thione-forming disulfides claimed. Thus, the teachings of *Goodman & Gilman* clearly support that the instant claimed invention is highly unpredictable.

(7). ***The Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support of the broad use of any compound represented by "thione-forming disulfides." As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 21 is indefinite because it is unclear what comprises a "potentially negative substituent". What makes a substituent potentially negative? A weak base? A strong base? Water? Carbonate? Butyl lithium? Sodium hydride? Does an alcohol qualify? What about a methyl group?

It is further noted that, for clarification purposes, a "negative ... substituent" would be better understood if it were described as a "negatively charged ... substituent".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 5-6, 10-12 and 17-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Henderson et al. (USPN 6001555) and as evidenced by Toth et al. (*Journal of Virology*, 67(10), 5879-88).

Henderson et al. discloses the treatment of retroviruses, such as HIV-1, with disulfides, such as 6,6'-dithiodinicotinic acid (Abstract; col. 2, line 16-col. 3, line 17; col. 13, lines 50-67; col. Col. 20, line 56-col. 21, line 40). Pharmaceutically acceptable carriers and formulations are disclosed (col. 14, lines 7-58).

It is noted, as evidenced by Toth et al., that the ability of NK cells to suppress HIV-1 is known in the art. See Abstract. Administration of the same composition to the same population will, inherently, have the same effect. In this case, administration of 6,6'-dithiodinicotinic acid to a patient for the treatment of HIV-1 will, inherently, modulate the NK cells of said patient and effect said treatment of HIV-1. It is not inventive to discover a new mechanism of action for a known method of treatment.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory W Mitchell whose telephone number is 571-272-2907. The examiner can normally be reached on M-F, 8:30 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

gwm

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER